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EDITORIAL COMMENT

Improving Risk Stratification for Heart Failure

A Role for Serial Testing of B-Type Natriuretic Peptides?*

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The growing burden of heart failure (HF) in the elderly population cannot be overstated (1–4). More than 9% of American men and close to 5% of women ages 60 to 79 years report a diagnosis of HF, whereas above the age of 80 years these figures increase to 13.8% and 12.2%, respectively (5). Increasing HF prevalence in the elderly population reflects a steady or increasing incidence and greater survival (6–8). Despite reports of decreasing rates of first HF hospitalization (9), the health care burden associated with HF is alarming: hospitalizations for HF in the U.S. exceeded 1.1 million in 2006 (up from 877,000 in 1996), and there were an estimated 3.4 million HF visits in the same year (5). As a result, the estimated direct and indirect health care costs for HF in the U.S. alone exceed $37 billion in 2009 (5). Projections into the middle part of this century suggest that as the population ages, the prevalence and cost of HF care will continue to increase (2).

See page 441

Early identification of subjects in HF stage A who are at risk of developing overt HF is therefore a key HF prevention strategy that is emphasized in current guidelines (1,2). This strategy rightly targets the optimal treatment of predisposing risk factors for HF, including hypertension, coronary artery disease, and diabetes (10–12). Although two-thirds of the population-attributable risk for new HF events can be related to conventional risk factors, a substantial portion of incident HF within the community is not readily explained by considering these factors alone (4,10,13,14). In the elderly population, in which HF poses specific challenges—including higher rates of preserved left ventricular ejection fraction and greater comorbidity attributable to renal dysfunction, anemia, and atrial fibrillation—prediction of incident HF based on conventional risk factors may be less reliable (15).

Consequently, there is great interest in whether biomarker testing can identify subjects at risk for new HF or cardiovascular events (13,14,16). Among the plethora of biomarkers contributing to HF pathophysiology, the B-type natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro–B-type natriuretic peptide [NT-proBNP]) have received much attention (17). It is intuitively appealing that these peptides secreted primarily from cardiac myocytes in response to volume or pressure overload should be accurate early markers of HF (17). This has proven true for acutely symptomatic patients, in whom plasma BNP/NT-proBNP levels are now firmly established as validated diagnostic markers for acute HF (1,17). Across the spectrum of HF stages, these peptides are independent predictors of HF events or mortality (17). Recent studies have shown that serial measurements of BNP or NT-proBNP provide incremental risk prediction in acute decompensated or chronic HF settings, with the most recent peptide measurement providing the greatest prognostic value (18,19).

A number of studies in the community setting have tested whether biomarker measurement at a single time point can improve the prediction of cardiovascular events (13,14). These studies show a modest improvement in detection of cardiovascular mortality by risk models that include biomarkers compared with models containing conventional risk factors and demographic data alone (13,14). Much of this improvement in risk stratification reflects more accurate classification of subjects with low biomarker levels who are less likely to suffer events despite the presence of conventional risk factors for cardiovascular disease (13).

In a study described in this issue of the *Journal*, deFilippi et al. (20) have taken the concept of biomarker testing for early detection a step further by evaluating whether serial measurement of NT-proBNP improved the prediction of incident HF and of cardiovascular mortality in elderly subjects participating in the CHS (Cardiovascular Health Study). Detailed data had already been collected at baseline and follow-up, and patients with established HF were excluded. The investigators measured NT-proBNP levels using stored plasma from 4,312 participants at baseline. During a median follow-up of 11.9 years, there were 2.6 new HF events per 100 person-years and 2.1 cardiovascular deaths per 100 person-years. Baseline NT-proBNP levels were independent predictors of clinical events, with an inflection point in risk at the 70th percentile corresponding to an NT-proBNP concentration of 190 pg/ml. After adjustment for conventional risk factors and echocardiographic data, the investigators noted a 2.5-fold higher risk of HF or cardiovascular death for subjects within the

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highest NT-proBNP quintile compared with those in the lowest quintile.

Within the select group of 2,975 participants with a further plasma sample taken at 3 years, the investigators showed that a second NT-proBNP level provided incremental prognostic value. The risk for future HF events or mortality could be further stratified by whether NT-proBNP levels increased or decreased at follow-up. The highest risk was seen in subjects with higher baseline NT-proBNP levels (>190 pg/ml) who had a >25% increase in peptide levels at follow-up, whereas subjects in whom peptide levels decreased by >25% had significantly lower risk. Even in subjects with a baseline level below 190 pg/ml, an increase in NT-proBNP levels at follow-up by >25% to a level higher than 190 pg/ml was associated with significantly higher risk of adverse clinical events.

Appropriately, the investigators tested the incremental value of baseline and follow-up NT-proBNP levels compared with prediction of HF or mortality based on conventional and demographic factors alone (21). First, they showed that addition of baseline and then follow-up NT-proBNP levels resulted in statistically significant improvements in the C-statistic derived from receiver-operator characteristic curve analysis. Second, and more helpfully, they showed that incorporation of baseline and follow-up NT-proBNP levels resulted in more accurate classification of 10-year risk for HF or mortality, with between 4.5% and 7.9% of subjects being more accurately classified when baseline and/or follow-up NT-proBNP levels were incorporated.

The current study is commendable in highlighting the concept of dynamic risk stratification based on serial assessment. The findings confirm a modest improvement in risk stratification by including a single measurement of NT-proBNP levels (13,14,16). The investigators take this a step further by showing that serial NT-proBNP measurement at a later time provides a further modest improvement in risk stratification. The relatively modest impact of NT-proBNP on risk prediction is likely to reflect several factors, including the impact of age and comorbidity, such as renal dysfunction, on NT-proBNP levels and the relatively low accuracy for detection of left ventricular systolic or diastolic dysfunction by these peptides (17). Whether the improvement in risk stratification achieved by performing serial NT-proBNP testing crosses a threshold of definite clinical value needs further evaluation, with particular consideration of the cost effectiveness of such a strategy (21). The latter will be influenced by event rates and to a larger extent by whether early detection using NT-proBNP levels can alter management to improve outcomes beyond those achieved by optimal treatment of conventional risk factors. The concept of using serial NT-proBNP levels to guide the management of established chronic HF therapy is the focus of several recent and ongoing studies (22,23). It is salient to note that this strategy had the least success in older subjects, in whom NT-proBNP levels and treatment choices may be influenced by comorbidity and other factors (22,23). The current study raises other questions, including the optimal time interval for serial biomarker testing and the relative change that best identifies a risk of future events. An interval of 3 years, as in this study, is reasonable when event rates are low, but may miss a proportion of events in high-risk subjects. The variability seen in NT-proBNP levels measured at an interval in stable individuals has been highlighted in a number of studies. This variability is in small part attributable to assay characteristics, but largely reflects biological variability as a result of factors influencing secretion and clearance of NT-proBNP (24). In elderly patients, these factors could include myocardial ischemia, changes in renal function, or neurohormonal factors, all of which may modify clinical outcome (24). The findings from this study and others suggest that changes in NT-proBNP parallel the risk of adverse clinical outcomes (18,19).

In the acute HF setting, a second peptide measurement after treatment or at discharge is almost always helpful (18). Should we now advocate serial NT-proBNP testing of elderly subjects in the community to improve screening and risk stratification for HF? The current study suggests that there may be a benefit from such a strategy, but leaves some questions unanswered. Its findings should encourage further research into the role of serial risk assessment for heart failure using biomarkers.

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